IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:	Nadkarni et al.	GROUP ART UNIT:	1615
SERIAL NO.:	09/731,349	CONFIRMATION NO.:	9200
EXAMINER:	Oh	ATTORNEY DOCKET NO.:	3362/0/US
FILED:	December 6, 2000		

TITLE: VALDECOXIB COMPOSITIONS

CERTIFICATE OF MAILING

I hereby certify that this communication and any recited enclosures are being deposited with the United States Postal Service as First Class Mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on August 17, 2004.

Linda K. Cooper

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August 17, 2004

BRIEF FOR APPELLANTS

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TABLE OF CONTENTS

TABLE OF AUTHORITIES

PATENTS

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BRIEF FOR APPELLANTS

This is an appeal from the final rejection of the above-identified application made in the Office action mailed July 17, 2003. A Notice of Appeal was mailed on December 17, 2003. The time for filing the instant brief has been extended to August 17, 2004, by payment of the extension of time as indicated in the enclosed Amendment Transmittal letter.

I. REAL PARTY IN INTEREST

The real party in interest is Pharmacia Corporation, owner of a 100 percent interest in the pending application.

II. RELATED APPEALS AND INTERFERENCES

Appellants are unaware of any pending appeals or interferences which may directly affect or be directly affected by, or have a bearing on, the Board's decision in the pending appeal.

III. STATUS OF CLAIMS

This is an appeal from the final rejection of pending claims 1, 3, 5-10, 19, and 20. The claims on appeal are set forth in full in the Appendix to this Brief.

IV. STATUS OF AMENDMENTS

An Amendment After Final Action was submitted via facsimile on March 5, 2004, wherein the following amendment to claim 1 was proposed:

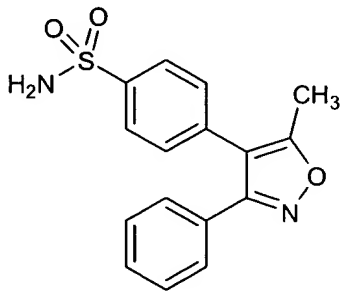
> 1. A discrete solid pharmaceutical composition ~~comprising~~ **consisting essentially of** particulate valdecoxib in an amount of about 5 mg to about 40 mg per dose and one or more pharmaceutically acceptable excipients, wherein a single oral administration of the composition in an amount containing about 20 mg of valdecoxib, to a fasting subject provides a time course of blood serum concentration of valdecoxib having a time to reach a concentration of 20 ng/ml not greater than about 0.5 h after administration.

This amendment has not been entered, and the listing of claims in the Appendix do not reflect this amendment.

No other amendments have been filed after the final rejection.

V. SUMMARY OF THE INVENTION

Valdecoxib (4-(5-methyl-3-phenyl-4-isoxazolyl)benzenesulfonamide) was disclosed in U.S. Patent No. 5,633,272 together with processes for preparing this and related compounds.[1] Valdecoxib has the structure:



[1] See Specification, page 1, lines 13-17.

Valdecoxib is a selective cyclooxygenase-2 (COX-2) inhibitor, and valdecoxib administration is indicated or potentially indicated in a very wide array of COX-2 mediated conditions and disorders.[2]

Valdecoxib has extremely low solubility in water. The formulations of the present invention, however, provide an orally deliverable dosage form of valdecoxib that exhibits good bioavailability and immediate-release properties.[3]

VI. ISSUES

The issues presented on appeal are (1) whether claims 1, 3, 5-7, 9, 10, 19, and 20 are unpatentable based on 35 U.S.C. §103(a) as being obvious over Black in view of Patel et al., Guess et al. and Bagchi et al.; and (2) whether claim 8 is unpatentable based on §103(a) as being obvious over Black in view of Patel et al., Guess et al., Bagchi et al., and Burch et al.

VII. GROUPING OF CLAIMS

For the purposes of this Appeal, claims 1, 3, 5-10, 19, and 20 do not stand or fall together. The claims have been divided into two groups: Group I (claims 1, 3, 5-7, 9, 10, 19, and 20) and Group II (claim 8). The claims of Groups I and II are separately and independently patentable for the reasons described in Section VIII(A), *infra*.

VIII. ARGUMENT

A. The Rejection of Claims 1, 3, 5-10, 19, and 20 as Unpatentable Under 35 U.S.C. §103(a) is Improper

As a preliminary matter, appellant repeats that they do not admit that Patel et al. or Guess et al. are prior art under 35 U.S.C. §102 and reserves the right to overcome this

[2] Id. at page 2, lines 9-20.
[3] Id.

characterization, by way of a 37 CFR. 1.131 declaration or otherwise. Assuming arguendo that Patel et al. and/or Guess et al. are available as prior art under 35 U.S.C. §102, Applicant respectfully traverses this rejection.

1. The Group I Claims (Claims 1, 3, 5-7, 9, 10, 19, and 20)

Claim 1 is representative of the Group I claims. Claim 1 is directed to a discrete solid pharmaceutical composition comprising particulate valdecoxib in an amount of about 5 mg to about 40 mg per dose and one or more pharmaceutically acceptable excipients, wherein a single oral administration of the composition, in an amount containing about 20 mg of valdecoxib, to a fasting subject provides a time course of blood serum concentration of valdecoxib having a time to reach a concentration of 20 ng/ml not greater than about 0.5 h after administration.

Black describes 2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one ("Compound A") as a COX-2 inhibitor, and describes formulations comprising this compound prepared via wet granulation with microcrystalline cellulose, lactose monohydrate, hydroxypropyl cellulose, croscarmellose sodium, and magnesium stearate.[4] Nowhere does Black even mention valdecoxib, much less suggest substituting valdecoxib or any other COX-2 inhibitor for Compound A in the compositions described therein. Furthermore, there is no indication of the physical properties of Compound A, and thus it is not apparent that valdecoxib may be successfully substituted for Compound A in the compositions Black describes.

Patel et al. describe pharmaceutical delivery systems for pharmaceutically active ingredients. In each embodiment discussed by Patel et al., the compositions include an encapsulation coat on a substrate; this encapsulation coat includes at least one

[4] See Example 2, page 17.

ionic or non-ionic hydrophilic surfactant,[5] and/or a lipophilic component.[6] One skilled in the art provided with this disclosure at the time of the instant invention would understand that this encapsulation coat (including at least one ionic or non-ionic hydrophilic surfactant and/or a lipophilic component) was essential in the compositions described by Patel et al., by improving dissolution and/or release of a hydrophobic drug such as valdecoxib, and would not have been motivated to prepare the claimed compositions. Unlike Patel et al.'s compositions, the claimed compositions exhibit therapeutically effective blood-drug levels of valdecoxib within a surprisingly short time after administration without requiring Patel et al.'s encapsulation coat.

Guess et al. describe methods for treating or preventing nonbacterial prostatitis in a patient comprising the administration of a tachykinin receptor antagonist. Guess et al. remark that the tachykinin receptor antagonist may be administered in combination with another therapeutic agent, including selective cyclooxygenase-2 inhibitors.[7] Suitable selective cyclooxygenase-2 inhibitors are listed, including valdecoxib.[8] The Office notes that Guess et al. "is relied upon as a teaching reference, solely in order to illustrate that valdecoxib is known in the prior art, as being among a group of selective COX-2 inhibitors."[9] Indeed, appellants have acknowledged that valdecoxib was known in the prior art as a selective COX-2 inhibitor prior to the filing of the instant application.[10]

Bagchi et al. describe chemical derivatization (i.e., formation of a chemical bond) of photographic coupler molecules

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[5] See col. 2, lines 58-63.
[6] See col. 3, lines 1-27.
[7] See col. 32, line 29 through col. 33, line 24.
[8] See col. 33, line 19.
[9] See Office Action dated July 17, 2003, page 3.
[10] See Specification, page 1, lines 13-21.

with a pharmaceutical agent as a means to prepare nanoparticulate dispersions of the pharmaceutical agent. Bagchi et al. list dozens of pharmaceutically useful chemical compositions that may be derivatized;[11] one example is anti-inflammatory compounds.[12] Nowhere do Bagchi et al. suggest derivatizing valdecoxib according to the processes they describe.

The Office asserts that the combination of Black, Patel et al., Guess et al., and Bagchi et al. renders claims 1, 3, 5-7, 9, 10, 19, and 20 obvious. Appellants respectfully disagree, and asserts that the Office has failed to establish that claims 1, 3, 5-7, 9, 10, 19, and 20 are *prima facie* obvious.

The cited references do not disclose every element of claims 1, 3, 5-7, 9, 10, 19, and 20. None of Black, Patel et al., Guess et al., or Bagchi et al. disclose a discrete solid pharmaceutical composition comprising about 5 mg to about 40 mg of particulate valdecoxib, as required by claim 1. Furthermore, none of Black, Patel et al., Guess et al., or Bagchi et al. discloses a discrete solid valdecoxib composition wherein a single oral administration of the composition, in an amount containing about 20 mg of valdecoxib, to a fasting subject provides a time to reach a valdecoxib blood serum concentration of 20 ng/ml of not greater than about 0.5 hours after administration, also as required by claim 1. Similarly, none of these references describe the additional features added by claims 3, 5-7, 9, 10, 19, and 20, which depend from claim 1.

Furthermore, the Office has not demonstrated that one skilled in the art would have been motivated to combine the cited references to arrive at the composition of claim 1. The Office asserts that "Black teaches compositions with specific COX-2 inhibitors as the active substance, along with suitable dosages," and that "[t]he benefit of a COX-2 inhibitor composition in a

[11] See col. 5, line 46 through col. 6, line 7.
[12] See col. 5, line 48.

once-a-day formulation is explained as well."[13] However, as previously noted, Black makes no mention of valdecoxib, and provides no details regarding the physical properties of the compound he does describe (Compound A). Without knowledge of these physical properties, one skilled in the art would have understood that the compositions Black described would not necessarily be successfully adapted for use with drugs other than Compound A. Indeed, Black indicates that Compound A is particularly suitable for once-a-day dosing due to its half-life:

> Not only is compound A active, potent, safe and effective at modest oral dosages of 10 to 250 mg of agent per day, but in addition Compound A possesses a half-life in humans of sufficient length that one or two oral doses of 10 to 250 mg of active agent per day will provide effective safe anti-inflammatory treatment over a 24 hour period.[14]

Thus, it is the half-life of Compound A, and not the particular formulation of the drug, that renders the compound suitable for once-a-day dosing. One skilled in the art would not expect a drug having a markedly different chemical structure than that of Compound A - for example, valdecoxib - to exhibit a similar half-life.

The Office has failed to show that one skilled in the art would have been motivated to combine the cited references. Black emphasizes that Compound A is particularly well-suited for formulation into the compositions they describe, and there is nothing in that reference, nor in Guess et al. (the only reference cited by the Office against claims 1, 3, 5-7, 9, 10, 19, and 20 that mentions valdecoxib) that substituting valdecoxib for Compound A would be desirable, much less successful in providing compositions having the properties set forth in claim 1.

For at least the foregoing reasons, the Office has not established that claims 1, 3, 5-7, 9, 10, 19, and 20 are *prima*

[13] See Office Action dated July 17, 2003, pages 3-4.

facie obvious over Black in view of Patel et al., Guess et al., and Bagchi et al., and appellant respectfully requests that the rejection of these claims be withdrawn.

2. The Group II Claims (Claim 8)

Claim 8 depends from claim 1, and is directed to a discrete solid pharmaceutical composition comprising particulate valdecoxib in an amount of about 5 mg to about 40 mg per dose and one or more pharmaceutically acceptable excipients, and further comprising one or more opioid or analgesic drugs, wherein a single oral administration of the composition, in an amount containing about 20 mg of valdecoxib, to a fasting subject provides a time course of blood serum concentration of valdecoxib having a time to reach a concentration of 20 ng/ml not greater than about 0.5 h after administration.

Burch et al. describe compositions comprising an opioid analgesic and a COX-2 inhibitor. Nowhere do Burch et al. describe the combination of valdecoxib with an opioid analgesic.

The Office has not made a *prima facie* case that claim 8 is obvious based on Black in view of Patel et al., Guess et al., Bagchi et al., and Burch et al. None of these references describe every element of claim 8. Furthermore, for the reasons given above, there is no motivation to combine Black, Patel et al., Guess et al., and Bagchi et al. to arrive at the composition of claim 8, and Burch et al. does not provide what is missing from the other references. Thus, appellant respectfully requests that the rejection of claim 8 be withdrawn.

B. Conclusion

For the foregoing reasons, appellants respectfully submit that claims 1, 3, 5-7, 9, 10, 19, and 20 are patentable over Black in view of Patel et al., Guess et al. and Bagchi et al.,

[14] See page 5, lines 22-26.

and that claim 8 is patentable over Black in view of Patel et al., Guess et al., Bagchi et al., and Burch et al., and request that the rejection of these claims as being unpatentable under 35 U.S.C. § 103(a) be reversed.

The Commissioner is hereby authorized to charge any fees which may be required to Deposit Account No. 19-1025.

Respectfully submitted,

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Enclosures:

Transmittal Letter
Fee Transmittal
Request for Extension of Time
Appeal Brief Transmittal
Itemized Postcard

APPENDIX - PENDING CLAIMS

1. A discrete solid pharmaceutical composition comprising particulate valdecoxib in an amount of about 5 mg to about 40 mg per dose and one or more pharmaceutically acceptable excipients, wherein a single oral administration of the composition, in an amount containing about 20 mg of valdecoxib, to a fasting subject provides a time course of blood serum concentration of valdecoxib having a time to reach a concentration of 20 ng/ml not greater than about 0.5 h after administration.

2. Cancelled.

3. The composition of Claim 1 wherein said time course of blood serum concentration of valdecoxib has a time to reach maximum concentration (T_{max}) not greater than about 3 h after administration and a maximum concentration (C_{max}) not less than about 100 ng/ml.

4. Cancelled.

5. The composition of Claim 1 that is a tablet wherein the excipients comprise one or more diluents in an amount of about 5% to about 99%, one or more disintegrants in an amount of about 0.2% to about 30%, one or more binding agents in an amount of about 0.5% to about 25%, and one or more lubricants in an amount of about 0.1% to about 10%, by weight of the composition.

6. The composition of Claim 5 wherein the binding agent is pregelatinized starch.

7. The composition of Claim 1 that is a tablet wherein the excipients comprise lactose monohydrate, microcrystalline

cellulose, croscarmellose sodium, pregelatinized starch and magnesium stearate.

8. The composition of Claim 1 further comprising one or more opioid or analgesic drugs.

9. The composition of Claim 1 wherein D_{90} of the valdecoxib particles is less than about 75 μm.

10. The composition of Claim 1 wherein the valdecoxib particles have a weight average particle size of about 1 to about 10 μm.

Claims 11-18: Cancelled.

19. A method of treating a medical condition or disorder in a subject where treatment with a cyclooxygenase-2 inhibitor is indicated, comprising orally administering to the subject a composition of Claim 1 one to about four times a day.

20. The method of Claim 19, wherein the composition is orally administered to the subject once or twice a day.